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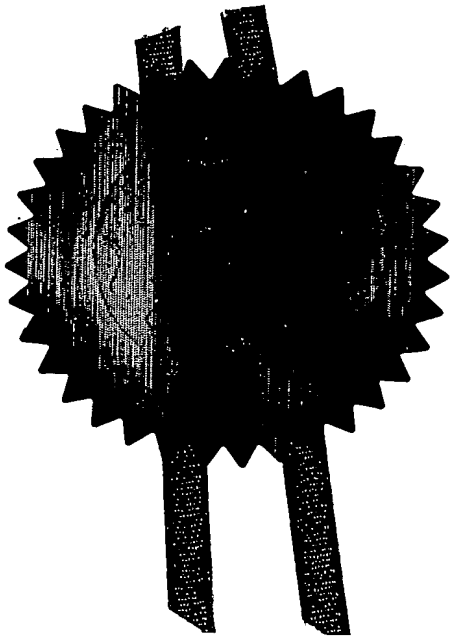

Signed R. Mahoney

Dated 26 May 2004

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17APR03 E800954-4 D00192
P01/7700 0.00-0308857.2

Request for grant of a patent

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1. Your reference — P88110 TAC

2. Patent application number
(The Patent Office will fill in this part) — 0308857.2 — 16 APR 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

George MARGETTS, 44 Broomfield Drive, Billingshurst, Sussex RH14 9TN 3214541001

Gavin Paul VINSON, 37 Birchwood Avenue, Muswell Hill, London N10 3BE 7585896001

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — TREATMENT OF ANGIOTENSIN II - INDUCED CARDIOVASCULAR DISEASE

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

J.A. KEMP & CO.

14 South Square
Gray's Inn
London
WC1R 5JJ

Patents ADP number *(if you know it)* 26001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

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Patents Form 1/77

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Continuation sheets of this form	0
Description	11
Claim *(s)*	4
Abstract	1
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature J.A. Kemp & Co Date 16 April 2003

J.A. KEMP & CO.

12. Name and daytime telephone number of person to contact in the United Kingdom

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Treatment of Angiotensin II-induced cardiovascular disease.

The present invention relates to the use of pharmaceutical compositions comprising trilostane or a related compound as active ingredient in the treatment of angiotensin II related cardiovascular disease.

Regulation of angiotensin II levels in the body is an important factor in both preventing cardiovascular disease and alleviating its effects. Angiotensin II produces several actions in the body, some of which lead directly to cardiovascular disease; others lead to the production of different hormones, for example mineralocorticoids such as aldosterone, which in turn cause the disease. The present invention relates to the use of trilostane, or related compounds, which have been found to modulate the action of angiotensin II receptors in the body, for treating cardiovascular disease.

Cardiovascular function is under the influence of a complex system of inter-related and inter-acting hormones that are released into the systemic circulation by various organs in the body. The renin-angiotensin-aldosterone (RAAS) system is one of the major hormone groups involved.

In this system the kidney secretes the proteolytic enzyme renin which acts on angiotensinogen, a plasma protein, splitting off a fragment containing 10 amino acids called angiotensin I. Angiotensin I is cleaved by a peptidase enzyme secreted by blood vessels, called angiotensin converting enzyme (ACE), producing angiotensin II, which contains 8 amino acids. Angiotensin II (Ang II) has a range of actions in the body, including constriction of the walls of arterioles, closing down capillary beds, stimulation of smooth muscle cell growth in the wall of arterioles thereby causing constriction, stimulation of the tubules in the kidney to reabsorb sodium ions and stimulation of the adrenal cortex to release aldosterone.

Aldosterone causes the kidneys to reclaim still more sodium and, thus, water, and increases the strength of the heartbeat and stimulates the pituitary to release the antidiuretic hormone (ADH, also known as arginine vasopressin).

In addition to the systemic role it is now believed that these hormones are also produced in the tissues of certain organs and act locally as well as at the systemic level. Although local

renin-angiotensin systems had been described as functionally distinct systems, recent experimental studies have suggested an association between hyperactivity of these local renin-angiotensin systems and cardiovascular dysfunction. For example, some studies indicate that the human cardiac renin-angiotensin system may be activated in heart disease. Furthermore, polymorphisms in genes coding for the renin-angiotensin system seem associated with hypertension and left ventricular hypertrophy (*Clin Exp Hypertens* 1995 Apr;17(3):441-68).

The existence of a local cardiovascular renin-angiotensin system (RAS) is often invoked to explain the long-term beneficial effects of RAS inhibitors in cardiovascular disease. However, it may be that not all the components of the RAS are synthesized *in situ*, so that local angiotensin II formation may occur independently of the circulating RAS. Local angiotensin formation in heart and vessel wall does occur, but may depend, at least under normal circumstances, on the uptake of renal renin from the circulation. Tissues may regulate their local angiotensin concentrations by varying the number of renin receptors and/or renin-binding proteins, the ACE level, the amount of metabolizing enzymes and the angiotensin receptor density. Binding of renin to cardiac vascular membranes may therefore be part of a mechanism by which renin is taken up from plasma.

In heart failure, aldosterone has been implicated in the formation of reactive interstitial fibrosis, a maladaptation that contributes to left ventricular remodeling. A recent study (*Endocrinology* 2002 Dec;143(12):4828-36) described the role of aldosterone in myocardial injury in a rat model. Angiotensin caused injury to the heart, including arterial fibrinoid necrosis, perivascular inflammation (primarily macrophages), and focal infarctions. Vascular lesions were associated with expression of the inflammatory mediators cyclooxygenase 2 (COX-2) and osteopontin in the media of coronary arteries. Myocardial injury, COX-2, and osteopontin expression were markedly attenuated by treatment with eplerenone (a new aldosterone blocker). The study concluded that aldosterone plays a major role in Ang II-induced vascular inflammation in the heart and implicated COX-2 and osteopontin as potential mediators of the damage. Somewhat similar findings were made in a study of the effects of eplerenone in dogs with chronic heart failure (*Circulation* 2002 Dec 3;106(23):2967-72). In this study heart failure was produced in dogs by intracoronary microembolizations that were discontinued when left ventricular (LV) ejection fraction (EF) was between 30% and 40%. In control dogs, LV end-diastolic and end-systolic volume

increased significantly. In contrast, end-diastolic volume, end-systolic volume, and EF remained unchanged during the 3 months of treatment with eplerenone. LV end-diastolic wall stress increased significantly in control dogs but decreased significantly in eplerenone-treated dogs. Compared with control, eplerenone was associated with a 28% reduction in cardiomyocyte cross-sectional area, a 37% reduction of volume fraction of reactive interstitial fibrosis, and a 34% reduction of volume fraction of replacement fibrosis. The study concluded that long-term therapy with eplerenone prevented progressive LV dysfunction and attenuated LV remodeling in dogs with chronic heart failure.

ACE inhibitors, in addition to their proven role in the treatment of hypertension, are used also for the treatment of cardiac failure. Clinical trials have shown that these agents, in addition to improving cardiac function, reduce mortality in heart failure. One therapeutic mechanism by which they treat heart failure is believed to be the reduction of circulating angiotensin II and aldosterone. However, the Renin-Angiotensin-Aldosterone axis (RAAS) is not uniformly suppressed during therapy for heart failure. This effect has been referred to as 'angiotensin II reactivation' which may herald clinical deterioration. In a large-scale clinical trial, referred to as the CONSENSUS I trial, correlations were seen between mortality, and angiotensin II and aldosterone. Furthermore, mortality was lower in those with good angiotensin II suppression. Therefore, it has been suggested (*Eur J Heart Fail* 1999 Dec;1(4):401-6) that neurohormonal elevation despite adequate treatment may associate with a poorer prognosis.

In the Randomized ALdactone Evaluation Study (RALES), spironolactone, an aldosterone receptor antagonist, significantly reduced mortality in patients with severe congestive heart failure (CHF). Spironolactone was given in addition to ACE inhibitors and its effect was additive to these agents (*J Am Coll Cardiol* 2002 Nov 6;40(9):1596-601)

Trilostane and Related Compounds

Trilostane, (4α,5α-17β)-4,5-epoxy-3,17-dihydroxyandrost-2-ene-2carbonitrile, is described in British Patent Specification No. 1,123.770 and in the U.S. Patent Specification No. 3,296,295.

GB 2,130,588 relates to an improved method of manufacture for trilostane and related compounds. This method allowed the micronising of the compounds to particles having a mean equivalent sphere volume diameter of from 5 to 12mm, with at least 95% of the particles having a particle size of less than 50mm. The greater specificity of particle size

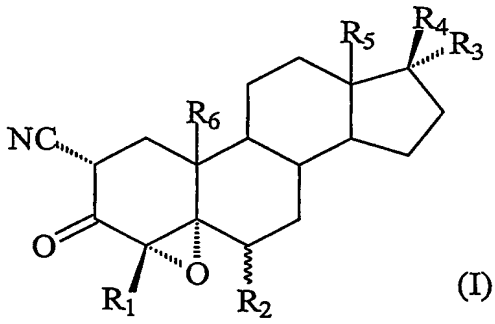
improves the bio-availability of trilostane and controls the amount of active metabolite formed, thus improving the clinical response and decreasing variability.

SUMMARY OF THE INVENTION

The inventors have surprisingly found that trilostane and related compounds inhibit the proliferative effects of angiotensin II on smooth vascular muscle cells, without necessarily lowering levels of mineralocorticoids, such as aldosterone, in the plasma thereby allowing treatment of proliferative diseases associated with these hormones. It is believed that the inhibition of the proliferative effects of angiotensin II on smooth vascular muscle cells, without necessarily lowering levels of mineralocorticoids, such as aldosterone, in the plasma arises through the reduction of sensitivity of angiotensin II receptors.

Accordingly the invention provides:

Use of a compound of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof in the manufacture of a medicament for the treatment of angiotensin II related cardiovascular disease in humans and animal

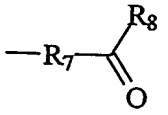


(I)

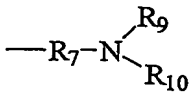
wherein R_1, R_2, R_5, R_6 are the same or different and each is hydrogen or $C_{1\ to\ 4}$ alkyl;

R_3 is hydrogen, $C_{1\ to\ 4}$ alkyl, $C_{1\ to\ 4}$ alkenyl or $C_{1\ to\ 4}$ alkynyl;

R_4 is hydroxyl, $C_{1\ to\ 4}$ alkanoyloxy, a group of formula (II) or (III)



(II)



(III)

wherein R_7 is $(CH_2)_n$, where n is an integer of from 0 to 4, R_8 is hydrogen, $C_{1\ to\ 4}$ alkyl, hydroxy or NH_2 and R_9 and R_{10} are the same or different and each is hydrogen or $C_{1\ to\ 4}$ alkyl; or R_3 and R_4 together are oxo, ethylenedioxy or propylenedioxy;

Use of a compound of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof in the manufacture of a medicament for the treatment of an angiotensin II related disease in humans and animals wherein the treatment is carried out in combination with the administration of one or more of:

- an Angiotensin Converting Enzyme (ACE) inhibitor;
- an angiotensin II receptor blocker; or
- an aldosterone inhibitor or agent for lowering aldosterone levels or blocking the effects of aldosterone;

A medicament comprising:

(a) a compound of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof; and

(b) one or more of:

- an ACE inhibitor;
- an angiotensin II receptor blocker; or
- an aldosterone inhibitor or agent for lowering aldosterone levels or blocking the effects of aldosterone;

A method of treating an angiotensin II related cardiovascular disease by administering to a patient having said disease a compound of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof in an amount effective to treat said disease; and

A method of treating an angiotensin II related cardiovascular disease by administering to a patient having said disease an amount of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof and an amount of one or more of:

- an ACE inhibitor;
- an angiotensin II receptor blocker; or
- an aldosterone inhibitor or agent for lowering aldosterone levels or blocking the effects of aldosterone

effective to treat said disease.

DETAILED DESCRIPTION OF THE INVENTION

Trilostane and related compounds as defined by formula (I) or 3-enol C_{1to4} alkanoate esters thereof may be used in the present invention.

Preferred compounds of formula (I) are those wherein R_1 is hydrogen or methyl, R_2 is hydrogen or methyl and R_5 and R_6 are methyl. It is further preferred that R_4 is hydroxy or R_3 and R_4 together are oxo. Examples of such preferred compounds are trilostane (R_1, R_2 and R_3 are hydrogen, R_4 is hydroxy and R_5 and R_6 are methyl), ketotrilostane (R_1 and R_2 are hydrogen, R_3 and R_4 together are oxo and R_5 and R_6 are methyl) and epostane (R_1, R_3, R_5 and R_6 are methyl, R_2 is hydrogen and R_4 is hydroxy.)

The present compounds may be used in the manufacture of a medicament for the treatment of angiotensin II related cardiovascular disease in humans and animals. Diseases which may be treated include, but are not restricted to, heart failure associated with proliferative and fibrotic changes such as congestive heart failure, post myocardial infarction, cardiomyopathy, diabetes, renal failure, metabolic syndrome (Syndrome X) and hyperaldosteronism such as primary, secondary and tertiary hyperaldosteronism and other diseases or conditions where increased levels of angiotensin II are present in the blood or the tissues of the body.

Such compounds are preferably used in particulate form. In particular, the compounds desirably consist of particles having a mean equivalent sphere volume diameter of 12 μm or less and 80, 85, 90, 95% or more, preferably 98% or more, 99% or more or 99.5% or more of the particles have a particle diameter of less than 50 μm, preferably less than 40 μm, less than 30 μm or less than 20 μm e.g. from 0.1 μm to 10, 20, 30, 40 or 50 μm, from 1 μm to 10, 20,

30, 40 or 50 μm or from 10 μm to 20, 30, 40 or 50 μm. The particles preferably have a mean equivalent sphere volume diameter of from 5 to 12 μm or of up to 5 μm, e.g from 0.1 to 5 μm or from 1 to 5 μm. It is further preferred that the cumulative percentage oversize versus size characteristic curve of the compound of formula (I) exhibits a standard deviation of from 1.5 to 2.5 μm, preferably from 1.75 to 2.25 μm, more preferably about 2 μm, e.g. 1.9 to 2.1 μm.

The treatment is given in the form of a medicament, which preferably comprises a unit dosage of from 25mg to 1000mg, for example from, 25 to 50mg, from 50 to 100mg, from 100 to 200mg, from 200 to 300mg, from 300 to 400mg, from 400 to 500mg, from 500 to 600mg, from 600 to 700mg, from 700 to 800mg, from 800 to 900 mg or from 900 to 1000mg, of the compound of the present invention. The medicament can be administered by an intravenous, intramuscular or subcutaneous route or topically as an ointment, cream or lotion. The preferred route is oral, for instance as a tablet, a capsule or a liquid dispersion.

The unit dosage described above may be administered at regular intervals such as one unit dosage administered once per month, once per week, once per day or several times per day. This treatment may be carried out for a total period of from one day, to several weeks, several months or for several years, for example for the rest of the subject's life.

Whilst trilostane and the other compounds of formula (I) and esters thereof may be administered in the pure form, usually they will be formulated with one or more pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or

mannitol and/or sorbitol. Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride. Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic solutions.

The treatment may be used alone or in combination with a further treatment of one or more compounds from the following; an ACE inhibitor, an angiotensin II receptor blocker or an aldosterone inhibitor or agent for lowering aldosterone levels or blocking the effects of aldosterone. The aldosterone inhibitor or agent for lowering aldosterone levels may or may not be an ACE inhibitor. Examples of suitable ACE inhibitors for use in the combination treatment include, but are not restricted to, Captopril, Enalopril and Lisinopril. Suitable aldosterone inhibitors or agents for lowering aldosterone levels include, but are not restricted to, Spironolactone, Losartan and Eplerenone.

The treatment and the further treatment may be carried out simultaneously, separately or sequentially, and in either order if separate or sequential. The treatment and further treatment may be given in the form of a single combined medicament, which preferably comprises a unit dosage of said further compound in an amount known in the art to be effective in the treatment of cardiovascular disease, and a unit dosage of a compound of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof in an amount as described above. The medicament may be administered by a mode as described above. Alternatively, the two treatments may be given separately or sequentially, e.g. as two different medicaments administered at the same site or at different sites, by the same mode of administration or by different modes of administration.

EXAMPLES

Aortic smooth muscle cells (ASMCs) were isolated from rat thoracic and abdominal artery (RASMC) and bovine aorta (BASMC) by the media explant method and cultured over several passages.

Segments of both abdominal and thoracic aortas were obtained from rats by careful dissection from killed rats. Segments of aorta were obtained from calves under anaesthesia. The segments of aorta were placed in a depression slide containing tissue culture medium, after which the adventitia and the outer portion of each segment was carefully removed under a dissecting microscope. The remaining inner portion of the tissue and the intima were removed to a separate dissecting dish and washed several times with fresh culture medium. At this point each segment was cut into approximately 1 mm squares and placed on 25 cm^2 tissue culture flask. The flasks were loosely capped and placed in a humidified CO_2 incubator After two hours, 4 ml of RPMI-1640 culture medium supplemented with 100 units/ml of penicillin, 100 mg/ml streptomycin, 4 pmol/L L-glutamine and 20% PBS was carefully added to the flasks without dislodging the tissue. Samples were fed with fresh medium after one week. The cells from the explants were relatively confluent within a period of approximately 2 weeks. They were then rinsed with PBS, and subsequently trypsinized with a solution of 0.125% trypsin and 0.02% EDTA in PBS for 1 -2 min al 37°C. The resulting suspension of cells was pipetted into 75 cm^2 tissue culture flasks containing 10 ml culture medium and incubated as above.

Experiments were performed with cells from passages 3 to 5.

Example 1

^{3}H-methylthymidine incorporation into rat aortic smooth muscle cells (RASMC). Quiescent RASMC (0.3 x 10^5/ml/well) were incubated with serum-free medium (SFM) containing Ang II (10^{-7} M) with or without different concentrations of trilostane for 48 hours. The results are shown in Table 1. ^{3}H-methylthymidine incorporation into RASMC was increased in the Ang II treated group. The tritium incorporation induced by Ang II was inhibited by trilostane at 10^{-7}6 and 10^{-5} but not at 10^{-9}, 10^{-8} and 10^{-7} M.

TABLE 1

Sample No.	Concentration of Ang II added to sample (M)	Concentration of Trilostane added to sample (M)	Tritiated thymidine uptake (dpm)
1	- (control)	- (control)	57.6
2	10^{-7}	-	87.1
3	10^{-7}	10^{-9}	96.7
4	10^{-7}	10^{-8}	101.88
5	10^{-7}	10^{-7}	89.1
6	10^{-7}	10^{-6}	74.9
7	10^{-7}	10^{-5}	42.7

Values are means ± S.E.M. N=3 per group. ANNOVA: P<0.001; Student's t-test – Comparison of controls with angiotensin simulated, P<0.01, Comparison of angiotensin stimulated with trilostane added at 10^{-6} or 10^{-5}M, P<0.05.

(dpm: disintergrations per minute)

Example 2.

Cell count for rat aortic smooth muscle cells (RASMC). RASMC (0.5×10^5/ml/well) were incubated with 20% FBS RPMI-1640 medium containing Ang II (10^{-7} M) with or without different concentrations of trilostane for 48 hours. The results are shown in Table 2. Number of RASMC in groups treated with Ang II 10^{-7} M was significantly increased, compared with controls. The Ang II stimulated increase in cell number was inhibited by trilostane at $10^{-6}$and 10^{-5} but not at 10^{-9}, 10^{-8} and 10^{-7} M.

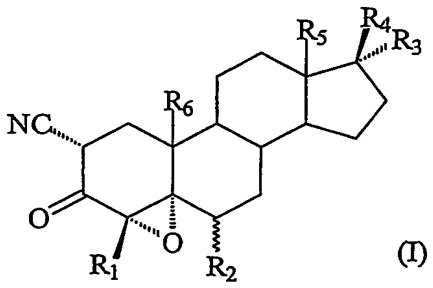
TABLE 2

Sample No.	Concentration of Ang II added to sample (M)	Concentration of Trilostane added to sample (M)	Cell Count
8	- (control)	- (control)	12.00×10^4
9	10^{-7}	-	21.30×10^4
10	10^{-7}	10^{-9}	21.00×10^4
11	10^{-7}	10^{-8}	21.95×10^4
12	10^{-7}	10^{-7}	20.00×10^4
13	10^{-7}	10^{-6}	14.00×10^4
14	10^{-7}	10^{-5}	14.25×10^4

Values are means ± S.E.M. N=3per group. ANOVA: P<0.001; Student's t-test- Comparison of controls with angiotensin stimulated, P<0.01, Comparison of angiotensin stimulated with trilostane added at 10^{-6} or 10^{-5}M, P<0.05.

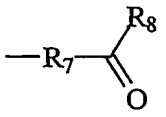
CLAIMS

1. Use of a compound of formula (I) or a 3-enol $C_{1\ to\ 4}$ alkanoate ester thereof in the manufacture of a medicament for the treatment of an angiotensin II related cardiovascular disease in humans and animals

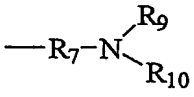


(I)

wherein R_1, R_2, R_5, R_6 are the same or different and each is hydrogen or $C_{1\ to\ 4}$ alkyl;
R_3 is hydrogen, $C_{1\ to\ 4}$ alkyl, $C_{1\ to\ 4}$ alkenyl or $C_{1\ to\ 4}$ alkynyl;
R_4 is hydroxyl, $C_{1\ to\ 4}$ alkanoyloxy, a group of formula (II) or (III)



(II)



(III)

wherein R_7 is $(CH_2)_n$, where n is an integer of from 0 to 4, R_8 is hydrogen, $C_{1\ to\ 4}$ alkyl, hydroxy or NH_2 and R_9 and R_{10} are the same or different and each is hydrogen or $C_{1\ to\ 4}$ alkyl; or R_3 and R_4 together are oxo, ethylenedioxy or propylenedioxy.

2. Use according to any one of claims 1 to 3, wherein in formula (I) R_1 is hydrogen or methyl and/or R_2 is hydrogen or methyl and/or R_4 is hydroxy or R_3 and R_4 together are oxo and/or R_5 and R_6 are methyl.

3. The compounds according to claim 2 wherein the compound of formula (I) is trilostane, ketotrilostane or epostane.

4. Use according to any one of claims 1 to 3 wherein the angiotensin II related cardiovascular disease is heart failure, congestive heart failure, post myocardial infarction, cardiomyopathy, diabetes, renal failure, metabolic syndrome (Syndrome X) and primary, secondary and tertiary hyperaldosteronism.

5. Use according to any of the preceding claims wherein the medicament comprises the compound of formula (I), as defined in claims 1 to 3, in particulate form.

6. Use according to claim 5 wherein the particles of the particulate form compound have a mean equivalent sphere volume diameter of up to 12 μm and 95% or more of the particles have a particle size of up to 50 μm.

7. Use according to claim 5 or claim 6 wherein the particles have a mean equivalent sphere volume diameter of from 5 to 12 μm.

8. Use according to any one of claims 5 to 7 wherein the particles have a mean equivalent sphere volume diameter of up to 5 μm.

9. Use according to any one of claims 5 to 8 wherein the specific surface area of the particulate compound is 2 m^2g^{-1} or higher or 5 m^2g^{-1} or higher.

10. Use according to any one of the preceding claims wherein the medicament is administered orally either as a tablet, a capsule or a liquid dispersion.

11. Use according of any one of the preceding claims wherein the medicament comprises a unit dosage of from 25 mg to 1000 mg of a compound of formula (I) or a 3-enol $C_{1\ to\ 4}$ alkanoate ester thereof as defined in claims 1 to 3.

12. Use according to claim 11 wherein the unit dosage is administered once per day.

13. Use according to any one of the preceding claims wherein the treatment of an angiotensin II related cardiovascular disease with a compound of formula (I) or a 3-enol $C_{1 \text{ to } 4}$ alkanoate ester thereof is carried out in combination with one or more of:

- an Angiotensin Converting Enzyme (ACE) inhibitor;
- an angiotensin II receptor blocker; or
- an aldosterone inhibitor or agent used for lowering aldosterone levels or blocking the effects of aldosterone in the body.

14. Use according to claim 13 wherein the inhibitor or agent used for lowering aldosterone levels is an ACE inhibitor.

15. Use according to claim 13 wherein the ACE inhibitor is Captopril, Enalopril or Lisinopril.

16. Use according to claim 13 wherein the aldosterone inhibitor or agent for blocking the effects of aldosterone is Spironolactone, Losartan or Eplerenone.

17. A medicament comprising:

(a) a compound of formula (I) or a 3-enol $C_{1 \text{ to } 4}$ alkanoate ester thereof as defined in claims 1 to 3 and 5 to 9; and

(b) one or more of:

- an ACE inhibitor;
- an angiotensin II receptor blocker; or
- an inhibitor or agent used for lowering aldosterone levels or blocking the effects of aldosterone

as defined in claims 13 to 16, for simultaneous, separate or sequential use in the treatment of an angiotensin II related cardiovascular disease as defined in claim 4.

18. A method of treating an angiotensin II related cardiovascular disease by administering to a patient having said disease an amount of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof as defined in any one of claims 1 to 3 in an amount effective to treat said disease.

19. A method of treating an angiotensin II related cardiovascular disease by administering to a patient having said disease an amount of formula (I) or a 3-enol C_{1to4} alkanoate ester thereof as defined in any of claims 1 to 3 and an amount of one or more of:

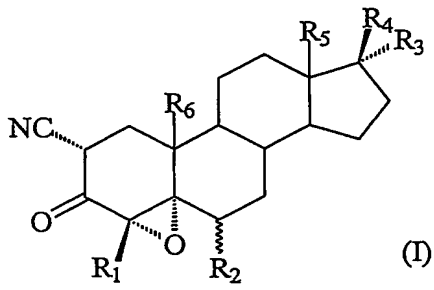
- an ACE inhibitor;
- an angiotensin II receptor blocker; or
- an aldosterone inhibitor or agent for lowering aldosterone levels or blocking the effects of aldosterone

effective to treat said disease.

ABSTRACT

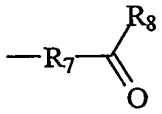
Treatment of Angiotensin II-induced cardiovascular disease.

Use of a compound of formula (I) or a 3-enol $C_{1\ to\ 4}$ alkanoate ester thereof in the manufacture of a medicament for the treatment of an angiotensin II related cardiovascular disease in humans and animals

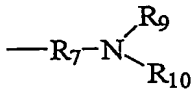


(I)

wherein R_1, R_2, R_5, R_6 are the same or different and each is hydrogen or $C_{1\ to\ 4}$ alkyl;
R_3 is hydrogen, $C_{1\ to\ 4}$ alkyl, $C_{1\ to\ 4}$ alkenyl or $C_{1\ to\ 4}$ alkynyl;
R_4 is hydroxyl, $C_{1\ to\ 4}$ alkanoyloxy, a group of formula (II) or (III)



(II)



(III)

wherein R_7 is $(CH_2)_n$, where n is an integer of from 0 to 4, R_8 is hydrogen, $C_{1\ to\ 4}$ alkyl, hydroxy or NH_2 and R_9 and R_{10} are the same or different and each is hydrogen or $C_{1\ to\ 4}$ alkyl; or R_3 and R_4 together are oxo, ethylenedioxy or propylenedioxy.